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Current Approaches of Tracers for Sentinel Lymph Node Mapping in Breast Cancer

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Abstract

Background: Sentinel lymph node (SLN) biopsy remains a cornerstone in the management of breast cancer, as it provides an accurate staging of the disease while minimizing the morbidity associated with complete axillary lymph node dissection. Advances in SLN detection have been very important in refining surgical techniques and improving patient outcomes. The purpose of the present study is to compare the effectiveness of radiocolloids, blue dyes, and fluorescent tracers in detecting the sentinel lymph node in breast cancer. **Materials and Methods:** Specifically, we analyzed the detection rate, accuracy, and safety profile of the techniques to outline the most reliable and clinically available. A comprehensive review was conducted, searching key databases, including PubMed, Scopus, and Web of Science, for studies published between 2010 and 2024. The review focused on studies that compared the performance of radiocolloids, blue dyes, and fluorescent tracers in the detection of sentinel lymph nodes in breast cancer patients. A total of 54 studies were included based on specific inclusion criteria. **Results:** Radiocolloids showed high detection rates in studies. Blue dyes have comparable results, but a small percentage of allergic reactions has been observed. Fluorescent tracers such as indocyanine green have improved visualization and accuracy, but their use requires specialized equipment and expertise. Combining radiocolloids with blue dyes or fluorescent tracers has improved detection rates in several studies. Cost and accessibility challenges have also been pointed out, particularly in low-resource settings. **Conclusions:** Radiocolloids have attained the status of gold standard in the detection of SLNs in breast cancer for their reliability and accuracy. While combined use with other tracers, like blue dyes or

fluorescent agents, enhances overall detection performance, making it more holistic. As expected, further innovation and effort are required to improve accessibility and optimize the technique of sentinel lymph node biopsy worldwide.

Keywords

Sentinel Lymph Nodes, Breast Cancer, Tracers

1. Introduction

Breast cancer is still the most common malignant tumor affecting women globally by incidence and mortality, remaining one of the major public health challenges worldwide. It accounts for 24.5% of all cancers in females and thus serves as a significant socioeconomic burden, along with the imposition of substantial psychological and physical pressure on patients [1]. Geographical variations in the incidence of breast cancer point to an interaction of risk factors, where exogenous factors like lifestyle, diet, and environmental exposures interact with genetic predispositions to contribute to susceptibility [2]. Such findings, therefore, provide evidence for the multifactorial etiology of breast cancer and the urgent need for comprehensive preventive strategies adapted to regional contexts. According to the World Health Organization, in 2022, there were 2.3 million women diagnosed with breast cancer and 670,000 deaths globally [3]. Although incidence rates are highest in high-income countries, the disease is becoming increasingly prevalent in low- and middle-income regions, driven by rising life expectancy, urbanization, and lifestyle changes [1].

While there has been improvement in the detection and treatment of the disease, a substantial inequality persists globally in the outcomes of breast cancer cases. Deaths are lower in higher-income countries because of organized screening programs, better access to treatments, and more developed healthcare facilities [3]. Many low- and middle-income countries lack adequate healthcare, have poor awareness, and are compelled to depend on late-stage diagnosis of the illness, factors that further increase mortality rates [4].

On the other hand, there are also biological factors that might contribute to disparities in outcomes. Such is the case with triple-negative breast cancer (TNBC), a globally aggressive subtype among women of African descent, associated with poor survival due to the limited availability of targeted treatments for this malignancy [5]. This calls for a deeper understanding of the biological and regional differences in the features of breast cancer as a means to improve results worldwide. These challenges would, therefore, be better addressed by directing global efforts toward increasing access to screening and treatment, raising awareness, and conducting further research in the realm of subtypes and outcomes of breast cancer across diverse populations. Such efforts might greatly reduce mortality from this disease and

improve the quality of care provided worldwide [6].

Breast cancer remains one of the most common malignancies for women of all geographic and ethnic backgrounds, offering a host of challenges in management particularly with regards to correct staging and over-treatment. While imaging and systemic therapy have transformed outcomes, effective surgical staging remains one of the cornerstones of personalized care. SLNB has emerged as a less invasive but highly sensitive alternative to ALND, with reduced risks of complications such as lymphedema and shoulder dysfunction.

However, the optimization of SLNB is one of the most important items in the agenda of improving the care of breast cancer patients. Challenges involve ensuring precise identification of SLNs, minimizing false negatives, and selecting the most appropriate tracers that enhance detection accuracy. Contemporary methods of SLNB balance the diagnostic efficacy with the safety of the patients by using everything from blue dyes to fluorescent agents, each with specific advantages and disadvantages. Success with such challenges places SLNB at the heart of the transition toward minimal invasion, and highly effective strategies in the management of breast cancer.

2. Materials and Methods

A literature review was carried out using three major medical and scientific databases: PubMed, Cochrane Library, and Scopus. Studies that specifically evaluated the efficacy of SLNB in breast cancer patients were targeted. The search strategy involved retrieving a wide spectrum of relevant research using the following keywords and keyword combinations: "sentinel lymph node biopsy", "breast cancer", and "tracers". These keywords were selected to express the variability inherent in SLNB techniques. Overall, 316 articles were identified in the preliminary search. Title and abstract screening were carried out, followed by the inclusion of studies that met the following criteria: the study included female patients diagnosed with early-stage breast cancer; SLNB techniques were compared using various types of tracers; and information on detection rate, accuracy, and clinical outcomes was provided. We excluded studies that referred to male breast cancer, malignancies other than breast cancer, or detection methods other than the use of tracers. Reviews, case reports, and non-original research were excluded unless they provided substantial data relevant to SLNB techniques. Fifty-four studies ultimately met these inclusion criteria based on full-text review. The extraction focused on the following: patient population characteristics, detection techniques, sensitivity and specificity of SLNB, and comparative effectiveness between different tracer combinations. To enhance transparency in the study selection process, a PRISMA flow diagram has been included to illustrate the identification, screening, eligibility, and inclusion stages of the literature review (**Figure 1**).

Besides, the methodological quality of the included studies was assessed based on the study design, sample size, and control groups; special attention was paid to randomized controlled trials and prospective studies. Where possible,

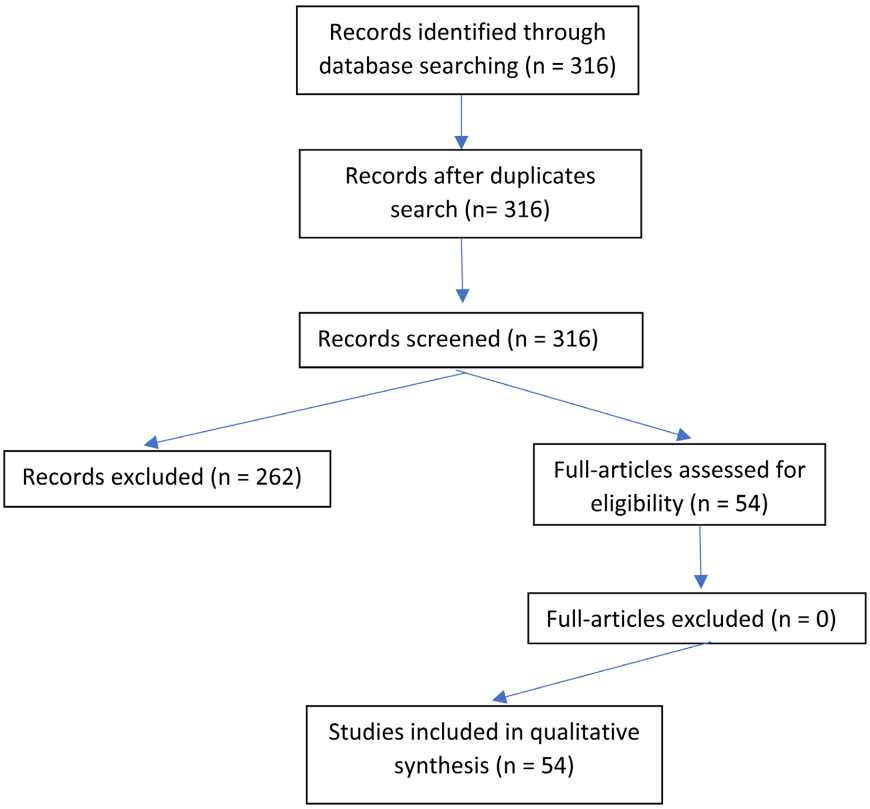

Figure 1. PRISMA flow diagram illustrating the study selection process for the review. Source: PRISMA 2020.

subgroup analyses were conducted to determine how SLNB performance might differ depending on the tracer agent. This review thus provides a sound synthesis of the current evidence on detection accuracy and clinical utility of tracers for the identification of sentinel lymph nodes in breast cancer patients.

3. Results

3.1. Genetic Mutations and Breast Cancer Risk

Well-known highly penetrant inherited gene mutations, such as BRCA1, BRCA2, and PALB2, increase the risk of the disease. For instance, risk-reducing strategies such as preventive mastectomy or chemoprevention can be considered and offered to women with mutations in these key genes [3]. Further, BRCA mutations have been strongly associated with susceptibility to TNBC, an aggressive subtype of cancer with no estrogen, progesterone, and human epidermal growth factor receptor 2 receptors, which would further render it unresponsive to any form of treatment. Young women with BRCA mutations are at an increased risk of TNBC, a type of breast cancer characterized by its aggressive behavior and poor differentiation [7]. Given these increased risks, several preventive measures such as chemoprevention or prophylactic mastectomy have also been strongly advised for women with BRCA mutations, among others with high-risk genetic mutations, to decrease their risk for breast cancer [8].

3.2. Biological Differences in Breast Cancer by Age

Generally, younger women with breast cancer have a different biological nature of the disease compared with those of an older age group. Indeed, there are some data from studies indicating the presence of age-related differences in tumor characteristics that suggest more aggressive disease in younger women. For example, a study demonstrated that breast cancer patients under the age of 45 were more likely to overexpress human epidermal growth factor receptor (HER2) and epidermal growth factor receptor but less likely to express estrogen and progesterone receptors [9]. All these findings suggest that in younger age groups, the disease may be biologically different and more aggressive, therefore requiring more aggressive treatment modalities.

3.3. Treatment Strategies by Stage and Molecular Profile

The strategy for treating breast cancer significantly differs according to the stage of diagnosis and molecular makeup of the tumor (**Figure 2**). It usually carries an exceptionally good prognosis in early-stage breast cancer, stage 0, confined either to the ducts or mammary glands, with an extremely low risk of involvement of lymph nodes. It carries only 1% - 2% lymph node involvement, and thus, appropriate treatment offers more than 98% long-term survival [10]. Surgical treatments for stage 0 breast cancer include mastectomy or breast-conserving surgery, a procedure in which the tumor is removed and as much breast tissue as possible is preserved. For tumors containing hormone receptors, adjuvant hormone therapy can further reduce the risk of recurrence. Tamoxifen plus annual screening ± magnetic resonance imaging versus no tamoxifen or screening resulted in a 40% reduction in the risk of invasive breast cancer and a 57% reduction in the risk of death from breast cancer [11].

Surgery forms the cornerstone of treatment in the management of stage 1 and stage 2 breast cancers, where tumors are usually small and may involve minimal lymph node spread. This may be followed by adjuvant therapies, which can involve chemotherapy, radiotherapy, or hormone therapy, depending on the molecular characteristics of the tumor. Categorization through immunohistochemistry allows the categorization of cancers into specific subtypes, based on the content of estrogen receptors, progesterone receptors, and HER2, along with the proliferation marker Ki-67. These molecular markers form the basis for most therapeutic decisions in the attempt to individualize treatment for the particular subtypes of the disease: Luminal A, Luminal B, HER2-positive, and triple-negative breast cancer [12].

Neoadjuvant chemotherapy is usually considered in more advanced stages of the disease, such as stage 3 breast cancer, with the aim of shrinking the tumor prior to surgery. This approach contributes to better surgical outcomes and could extend the chances for breast-conserving surgery [13]. Treatment in stage 4 metastatic breast cancers shifts toward systemic therapies directed at the control of disease for symptom alleviation and prolongation of patient survival. Newer

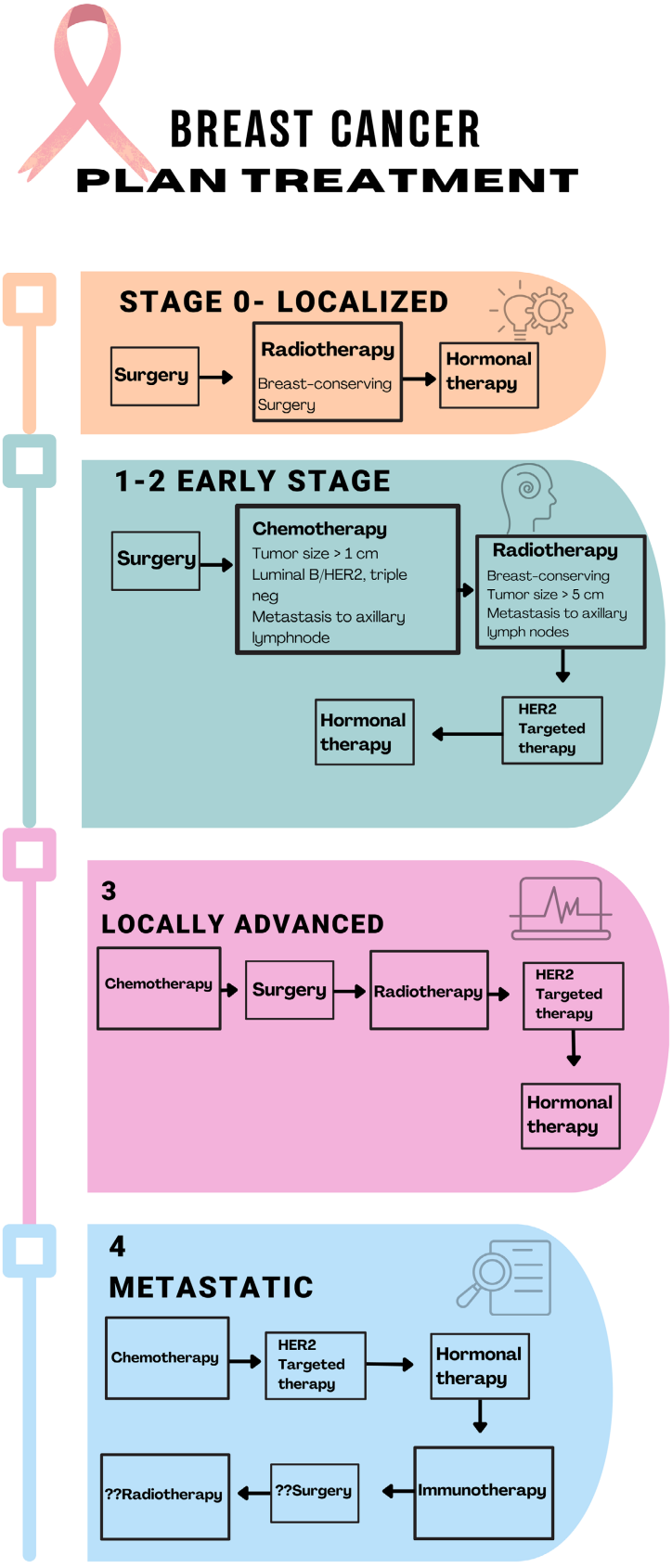

Figure 2. Breast cancer treatment plan: stages and therapeutic options.

therapeutic approaches, including HER2-targeted treatments, immunotherapy, and personalized medicine, have expanded options for patients with advanced disease and offer hope for improved outcomes in this challenging setting [14].

3.3.1. Axillary lymphadenectomy

Axillary lymphadenectomy, or axillary dissection, remains a cornerstone in the surgical treatment of breast cancer, especially for staging and controlling locoregional disease. The procedure may be done through a separate incision at the base of the axilla, following the natural fold of the skin at the hairline, or by extending the elliptical incision that is commonly used for a modified radical mastectomy (Madden type). Incisions are mainly designed based on surgical indications, extent of the tumor, and the patient's preference for either breast conservation or mastectomy treatment [15]. In cases of a negative SLNB with macroscopically suspicious lymph nodes, partial or lower axillary lymphadenectomy is commonly performed. This includes resection of lymph nodes from Berg's levels I and II, offering an excellent balance between adequate oncologic control and the lesser invasiveness of the procedure [16].

The presence of complex anatomical structures in the axilla creates significant technical difficulties in performing axillary lymphadenectomy. The destruction of lymphatic tissue interferes with both lymphatic and neural pathways. The most common intraoperative complication is damage to the axillary vein; while vascular repair is possible, extensive parietal injuries of the vein promote embolism and destroy the integrity of the venous wall. In such cases, ligation of the axillary vein is indicated; however, this is associated with a significant risk of postoperative lymphedema, which might result in long-term functional impairment [15].

Another important aspect of the operation is to maintain the integrity of the intercostal musculature. The intercostal musculature can be accidentally damaged and may lead to pleural perforation, which can be a serious complication that needs to be avoided with cautious dissection. Hemostasis is crucial intraoperatively and postoperatively, as both intraoperative and postoperative bleeding can occur. However, perhaps the most significant long-term complication remains lymphedema. This neuropathic condition can lead to no functional impairment at all or quite severe degrees, and is generally accompanied by paresthesia and breast edema, particularly in the case of breast-conserving surgery [17].

3.3.2. SLNB and Its Advantages over Complete Axillary Lymphadenectomy

SLNB has been recognized as a less invasive yet highly reliable method for evaluating lymph node status in breast cancer patients. SLNB focuses on the first-order lymph nodes that drain the tumor, thereby allowing lymph node excision only in selected cases. This approach minimizes the higher risk of complications—lymphedema, for example—associated with more extensive axillary lymphadenectomy [18].

The theory of the sentinel lymph node is based on the presence of a step-by-step dissemination of tumor cells through the lymphatic system, initially invading

the lymph node that directly drains the tumor, *i.e.*, the sentinel node. By identifying and biopsying this node, clinicians can determine whether cancer has spread and decide if further axillary surgery is required. Confirmation of metastasis is done through further management via immunohistochemistry and histopathological examination [19].

Axillary lymphadenectomy has been considered the gold standard in the staging of breast cancer. However, recent studies have found that in most cases, SLNB can safely eliminate the need for full axillary dissection. Prospective randomized trials, such as the IBCSG 23-01 and ACOSOG Z0011, showed that in early-stage breast cancer patients with a positive sentinel node, axillary lymphadenectomy could be omitted without affecting survival [20] [21]. Furthermore, it was clarified in the ACOSOG Z0011 trial that patients with T1-T2 breast cancers and clinically negative lymph nodes did not need axillary dissection, even in cases of positive sentinel nodes, provided no more than two sentinel nodes were positive [20].

This was further confirmed in the EORTC-AMAROS trial, which showed that disease outcomes for positive-sentinel-node patients receiving axillary radiation were comparable to those receiving axillary lymphadenectomy, but with markedly reduced morbidity [22]. It was also stated in the SOUND trial that for a selected group of patients with early-stage breast cancer, axillary ultrasound may be sufficient instead of SLNB, thus avoiding surgery for patients without suspicious nodes [23] [24].

3.3.3. Lymph Node Mapping Tracers

Accurate sentinel lymph node mapping is very important for the early diagnosis and effective treatment of cancer. Different kinds of tracers, such as blue dyes, radiocolloids, and superparamagnetic iron oxide nanoparticles (SPIOs), have become routine approaches in SLNB. 99mTc is one of the most commonly used radiotracers, with quite high sensitivity in the detection of sentinel nodes, whose detection rate is almost 100% if combined with a hand-held gamma probe [18].

Over the last decade, indocyanine green (ICG), a fluorescent dye, has gained wide acceptance as an alternative to blue dye. Various studies have reflected a sensitivity rate of 95% - 100% regarding the detection of sentinel lymph nodes by ICG, proving to be an option for breast cancer patients, especially under conditions where minimizing invasiveness is the key factor [25].

The success of SLNB is heavily reliant on the usage of specific markers that are designed to bind to lymphatic tissue and identify the sentinel lymph node. Appreciation of the factors affecting the success of SLNB requires an in-depth look at the molecular mechanisms of the tracer's behavior. Tracer uptake by tumor cells may be influenced by various factors, including the expression of cell surface receptors such as HER2 and estrogen receptors. This molecular interaction plays an important role in biopsy efficiency because higher affinity between the tracer and tumor cells could enhance tracer accumulation in the sentinel lymph node. Besides, tumor microenvironment contributes to tracer distribution. The presence of lymphatic vessels, immune cells, and extracellular matrix components modulates

how tracers spread through the tissue, influencing both the accuracy of detection and the accuracy of targeting. These factors vary between subtypes of breast cancer as well and may act to further refine the behavior of a tracer in the SLNB approach, potentially subtype-specific. Such features include different uptake patterns of a tracer in, for instance, HER2-positive tumors compared to hormone receptor-positive or triple-negative breast cancers; these might affect sensitivity in such subgroups.

The expanding roles of these advanced tracers, coupled with newer modalities for sentinel node detection, mark the shaping of refinement in breast cancer surgery toward the ultimate goals of precise staging with minimization of complications and improvement in patient outcomes.

1) Radiocolloids

Radiocolloids have considerably refined lymphatic mapping in the management of breast cancer, as well as other malignancies, by significantly raising the precision and reliability of SLNB. It was first suggested by Krag *et al.* in 1993, and the radiocolloid technique remains one of the most modern ways of detecting the sentinel node, where radiolabeled nanoparticles are used [26].

The most commonly used nanoparticles are those labeled with 99mTc, which has great advantages concerning ease of use, low cost, and applicability to non-invasive techniques such as single photon emission computed tomography (SPECT). SPECT has, in particular, evolved as a vital modality in clinical imaging and allows detailed whole-body imaging, which enhances diagnostic accuracy with minimal distress to the patient [27].

Radiolabeling strategies involving 99mTc have remained at the cutting edge of both diagnostic and therapeutic innovation. Such strategies improve not only lymphatic pathway visualization but also the precision of tumor staging and further treatment planning. That is why radiolabeling of bionanomaterials by using 99mTc has become a promising approach, considering the special chemical properties of technetium, among which one can mention the ability to form a great number of stable complexes with advantageous biological properties [28].

This is accomplished by the flexibility of the chemical coordination, allowing for the elaboration of molecular probes and radiotracers capable of a very fast assessment with high specificity and sensitivity for organ functionality, tissue perfusion, and diseases. Advances in the coordination chemistry of technetium, together with the improvement of detector technology, have significantly advanced the spatial resolution of SPECT.

These enhancements have brought SPECT closer to positron emission tomography with regard to image clarity and diagnostic power, and their role in lymphatic mapping and sentinel node detection in breast cancer is further consolidated [27]. The fact that radiocolloids can be incorporated into clinical practice with such accuracy means that not only is the detection rate of sentinel lymph nodes improved, but the necessity for further invasive techniques is diminished, thus benefiting patient outcomes.

2) Blue Dyes

Blue dye techniques constitute one of the oldest approaches to sentinel lymph node identification in melanoma and breast cancer. There are presently a number of shades of blue dye in use: methylene blue, isosulfan blue, and Patent Blue V. All have their own merits, but the most interest has been in methylene blue, showing a considerably lower false-negative rate compared with isosulfan blue and Patent Blue V [29]. Although the success rate has been high in many instances, such as identifying sentinel lymph nodes in as high as 96% of cases, the highest sensitivity and accuracy are obtained when the use of blue dyes is combined with that of a radiocolloid [30]. The dual approach, sometimes also referred to as a "dual tracer technique", provides the added visual benefit of blue dye along with the precision of a radiolabeled tracer to provide an identification rate that approaches 100%. One of the continual risks of the blue dye techniques, related in particular to isosulfan blue and Patent Blue V, is adverse reactions ranging up to anaphylaxis. This is a risk that will increase as sentinel lymph node biopsy becomes more common. Because of these issues, blue dye still plays a crucial role in lymphatic mapping, especially in situations where the use of radiocolloid is not possible or in cases that depend on the rapid detection of the sentinel nodes [30].

3) ICG

Recently, ICG has emerged as one of the highly successful alternatives to blue dye and radiocolloid in mapping the sentinel lymph nodes because of its less invasive and safer usage. It is a fluorescent dye that binds to albumin and is metabolized in the liver, rendering it biologically inert and non-toxic. Since its introduction into clinical practice in the mid-1950s, ICG has gained a wide range of applications in various medical fields, including cardiology and ophthalmology, due to its excellent safety profile [31].

In the context of breast cancer, ICG has become a useful tracer for SLNB. The fluorescence-guided detection provides better contrast visually intraoperatively, allowing surgeons to precisely locate the sentinel lymph nodes without radioactive materials. Although the gold standard has conventionally been the combination of blue dye and radiocolloid for SLNB, the increasing allergic reactions from blue dye and regulatory and safety challenges in handling radioactive isotopes have shifted interest toward alternative tracers such as ICG [31].

Recent studies have reported that ICG shows higher sensitivity and specificity compared to blue dye; detection rates in some series are equal to those seen with the combined use of blue dye and radiocolloid. Moreover, ICG's real-time fluorescence imaging provides more precise intraoperative surgical excision of the sentinel nodes without compromising too much tissue, thus minimizing the risk for lymphedema post-surgery [31]. ICG and radioisotope in combination result in higher identification rates, 97.2% versus 87.3%, with both decreasing skin discoloration related to blue dye. Specific recommendations concerning SLNB in breast cancer also contribute to the increasing popularity of ICG in clinical settings [32]. Thus, while more evidence of ICG's efficacy is accumulated, this drug

is on its way to achieving a status as one of the standard options to traditional tracers in SLNB, especially in indications where patient risk minimization and procedural efficiency are top priorities.

4) SPIOs

SPIOs could represent a potentially promising alternative in the detection of SLNs in breast cancer, showing some advantages compared to the traditional techniques represented by the blue dye and radioactive tracers. These nanoparticles take advantage of their magnetic properties to accumulate in the SLN and thus could be visualized by magnetic resonance imaging and allow precise and non-invasive localization [33]. With detection rates of 97.2%, SPIOs do not involve the use of radiation, hence are safer, particularly when a patient requires repeated imaging sessions [34]. SPIOs are capable of detecting the SLN located at depths of 30 - 40 mm or more, thus reaching nodes that are far from the facility of standard tracers. Because they act based on magnetic properties and not radioactive decay, SPIOs offer a radiation-free alternative and reach detection sensitivities equal to or higher than conventional techniques. This makes SPIOs particularly safe for patients who would undergo multiple imaging sessions [35]. SPIOs can also allow for intraoperative real-time tracking, thereby further increasing the accuracy of SLNB and decreasing the potential for a false-positive result [36]. The superparamagnetic iron oxide tracer Magtrace, combined with the detection system Sentimag, a handheld magnetic probe, represents a new approach to performing sentinel lymph node biopsy in early-stage breast cancer. It provides detection rates similar to radiocolloids and vital blue dyes but simultaneously offers some specific advantages and disadvantages, requiring knowledge of its particular features for its adequate application [37].

Table 1 provides a comparative overview of the key advantages and disadvantages associated with commonly used mapping tracers in sentinel lymph node biopsy for breast cancer. This comparison aims to guide clinical decision-making based on tracer efficacy, safety, and practicality.

Table 1. Advantages and disadvantages of tracers for sentinel lymph node biopsy.

Tracers	Advantages	Disadvantages
Radiocolloids	High detection rate Preoperative assessment Extensive use	Radiation exposure risk Delayed detection
Blue Dyes	Prompt detection Cost-effective	Suboptimal visualization Reduced detection rate Allergic events
Superparamagnetic iron oxide nanoparticles	No radiation Real-time tracking High accuracy	Costly Less available Limited for deep nodes
Indocyanine Green	High detection rate Real-time imaging Radiation free	Device cost Insufficient tissue penetration

3.4. SLNB

SLNB is very sensitive regarding the presence of cancer in lymph nodes, reaching an accuracy of 100% for dual tracers, 99.4% for radioisotope, and 89.1% for blue dye [38]. The popularity of this technique is due not only to its high diagnostic precision but also its cost-effectiveness and the relatively simple procedure involved in the identification of the sentinel nodes. Accurately identifying the first lymph node that drains from the tumor site is crucially important in the staging of breast cancer and in subsequent appropriate treatment.

Despite its many advantages, a number of limitations affect the overall efficacy of SLNB. Rates of sentinel node identification may vary and may be further compromised in some patients, leading to potential missed opportunities for accurate staging. Additionally, the internal mammary sentinel node is usually missed; the reason for this might be that the lymphatics of the anterior thoracic dermis drain predominantly to the axillae and may therefore lead to an underestimate of the disease burden in some patients. Further, allergic complications that might complicate the procedure and the management of the patient may arise from dye administration during SLNB. Another important limitation concerns the relatively narrow identification window for the tracer, where several studies suggest that the dye can "wash out" following injection and thus require surgically timely intervention [39].

Effective employment of radioactive tracers in SLNB depends upon successful interdisciplinary interaction between specialists in nuclear medicine, surgical oncology, and pathology. The radioactive tracer employed in SLNB is composed of a radioactive isotope that is conjugated to a colloidal substance. The selection of a tracer is based on various factors such as energy release of the isotope, half-life of the isotope, and injected dose. Each of these parameters has the capacity to drastically alter the efficiency of a tracer in locating sentinel nodes. After peritumoral administration, the radioactivity is taken up by lymphatic vessels and transported, via lymph flow, through the first lymph node receiving lymph directly from the tumor, which is called the sentinel node. In this lymph node, the colloid is taken in by macrophages and forms a high concentration of the tracer. The outcome is an efficient entrapment of the radioactive material within this lymph node, without bypassing to the lymph nodes downstream. The combination of vital dyes with radioactive tracers in sentinel node identification significantly enhances intraoperative detection rates. It improves not only the overall accuracy of the procedure but also makes the learning curve easier to overcome when mastering SLNB. Taken together, these approaches enable surgeons to further refine the technique so that patients undergoing treatment for breast cancer can be assured of more reliable outcomes.

4. Discussion

Methods of breast cancer sentinel lymph node mapping have significantly evolved over the last few years, with a focus on heightened accuracy and minimally invasive techniques. The evolution of surgical management for early-stage breast

cancer has indeed been a game-changing clinical practice, especially with the establishment of SLNB as the standard approach for axillary staging.

A combination with different tracers, for example, ICG and radiocolloid or SPIOs and blue dye, achieves certain advantages: an improvement in the rates of detection, precision, and SLN determination. Perhaps dual-tracer protocols allow both these tracers' complementary strengths to compensate for the relative shortcomings with regard to one marker methodologically for a reliable and as accurate as possible assessment of lymphatic involvement. Detection rates seem to be somewhat higher for ICG and radiocolloid combinations, with ICG offering real-time visual guidance and radiocolloid improving the accuracy of subsequent imaging. On the other hand, SPIO and blue dye protocols have also been effective, especially in those cases where MRI might be available for SPIO detection, although with lower resolution compared to the ICG-based combination. From a cost perspective the ICG and radiocolloid protocols can be little more expensive than others at times because special equipment is necessary to begin them, but usage of SPIO + blue dye is sometimes cheaper; blue dye costs very little money, and special imaging technologies have not been necessary for SPIO. However, from the overall cost-effectiveness perspective, one has to take into consideration the likely improved clinical outcomes of dual-tracer protocols, which may well reduce rates of false negatives and unnecessary reoperations.

This study highlights the critical role of sentinel lymph node biopsy in the accurate detection of lymph node involvement, which has been reported to exceed 90% in the literature. Clearly, such high efficacy enhances staging accuracy and supports treatment strategy determination, making SLNB an essential part of breast cancer management. Despite the successes noted here, our results indicate important limitations inherent to SLNB. Variability in identification rates has been emphasized to underscore the need for continued refinement of this technique. Therefore, the detectability of internal mammary sentinel nodes—due to their drainage pathways—remains an ongoing clinical challenge. This limitation underscores the need for surgeons to maintain a high index of suspicion and consider comprehensive imaging strategies when assessing nodal involvement, particularly in complex cases.

It is, therefore, justified to consider a balanced selection of patients for SLNB, as larger tumor size, aggressive immunohistochemical profiles, and younger patient age are associated with a higher risk of nodal invasion. A better selection can be achieved by guiding clinical judgment with these risk factors and tailoring interventions accordingly, as our analysis suggests. This challenges traditional paradigms and favors a more conservative approach to surgery, particularly with recent evidence indicating that complete axillary lymphadenectomy may not be justified in patients with micrometastases in the sentinel node. Indeed, this trend aims not only to reduce the physical and psychological burdens of extensive surgery but also to follow the principles of modern personalized medicine. Imaging-guided biopsy techniques in patients with T2N0M0 breast cancer may be a

rewarding strategy to further improve surgical outcomes.

The cost-effectiveness and global access to tracers, particularly in low-resource settings, shall be put to consideration. Despite the tremendous progress that tracers such as ICG and SPIO have brought with them in regard to SLNB, their usage in low-resource settings faces certain barriers to assimilation. This, coupled with the need for specialized equipment-such as near-infrared imaging in the case of ICG and MRI for SPIO-makes these reagents unavailable in most healthcare systems, especially in low-income countries. It is likely that high costs for both tracers and diagnostic technologies will be a major obstacle to the widespread use of SLNB. This does create a challenge in developing countries due to limited availability of advanced technology for treatment purposes. As and where appropriate, these alternative, low-cost tracers have to be tested for enabling correct staging as well as treatment for patients with carcinomas of the breast. Each of these challenges will have to be overcome through subsidies that may go toward tracers, the development of local manufacturing capacity, and access to diagnostic technologies in general.

Our findings highlight the importance of a multidisciplinary team consisting of surgeons, oncologists, radiologists, and radiation therapists. This cooperation is essential for formulating and applying a specific treatment protocol, which needs to be tailor-made for each patient to achieve optimized care and possibly improved long-term outcomes. The search for new imaging modalities and biomarkers is relevant in our efforts to address some of the shortcomings of current approaches to SLNB. The deeper our understanding of the molecular and biological underpinnings of the disease, the more vital it becomes to translate this knowledge into clinical workflows to improve sentinel lymph node detection and patient stratification.

Future studies should focus on further delineating the criteria for SLNB applicability, especially in the setting of micrometastases, to establish stringent guidelines that maximize patient management while minimizing unnecessary interventions. Moreover, the necessity of conducting larger, multi-center studies to test long-term outcomes following less invasive techniques cannot be overemphasized. Further research on the effectiveness of targeted therapies and observation policies, particularly in specific patient groups, is needed to help inform emerging practice patterns. This will greatly improve the quality of life for breast cancer patients by reducing morbidity from extensive surgical procedures. While SLNB has revolutionized the management of early-stage breast cancer, ongoing improvement is essential to optimize patient outcomes. Interdisciplinary collaboration and the integration of novel imaging and innovative therapeutic approaches can provide personalized and effective management of breast cancer.

This commitment to translating the latest research findings into clinical practice not only promises better clinical outcomes but also reflects a growing commitment to patient-centered care in the ongoing fight against breast cancer. SLNB plays a crucial role; it serves as a predictive tool for recurrence and survival, thus

guiding oncologists in treatment decisions. Compared to full axillary dissection, it minimizes surgical complications and side effects.

5. Conclusion

Identification and biopsy of the SLNB are cornerstones in the surgical management of early breast cancer, allowing for a minimally invasive approach that reduces morbidity without compromising diagnostic accuracy. Axillary lymphadenectomy remains a valid alternative in cases where SLNB is not feasible, but it carries higher risks. Larger tumor size, an aggressive profile, and younger age are important determinants of nodal invasion risk that guide surgical decisions. Timely axillary lymphadenectomy in cases with positive sentinel nodes seems to be indicated, but the approach should be individualized according to tumor characteristics. Implementation of image-guided biopsies in T2N0M0 patients within a multidisciplinary platform may offer better results. This approach will lead to more tailored therapy, with advanced imaging becoming a key part of this multidisciplinary strategy. The better the prognosis, the more optimal the care will be, ultimately improving breast cancer management and survival rates.

6. Future Perspectives

Despite advances in the treatment of breast cancer, few studies have explored the optimal method for evaluating the SLN, particularly for extending this principle into more general clinical practice outside of early-stage tumors. There is also no standard treatment protocol, as various factors such as age, tumor grade, and other biological features come into play.

Further studies are needed to optimize SLN biopsy criteria, specifically for micrometastases, and to introduce advanced imaging techniques and biomarkers to improve diagnostic accuracy and patient selection. Long-term results of less invasive strategies should be assessed through extensive multicenter studies, focusing on targeted therapies and selective observation while minimizing complications without compromising treatment efficacy.

The future of SLN mapping in breast cancer looks promising, with continuous improvements in imaging techniques and tracer methodologies. The application of dual-tracer methods and non-radioactive imaging systems has contributed to improved detection rates and a reduction in complications associated with traditional modalities. These advancements will promote personalized and effective management of breast cancer, leading to better overall outcomes and enhanced quality of life.

Authors' Contributions

Conceptualization, M.H.R. and E.C..; methodology, R.C.; software, D.E.L.; validation, E.C., M.R.H. and I.I.U..; formal analysis, R.C.; investigation, L.A.S.; resources, D.G.S.; data R.C.; writing—M.H.R.; writing—review and editing, E.C.; visualization, D.E.L.; supervision, E.C.; project administration, D.G.S. and L.A.S.

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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